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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GLENN FRANCIS BROWNING,
PHILIP FRANCIS MARKHAM, and CHI-WEN TSENG

Appeal 2016-004149
Application 13/202,534[1]
Technology Center 1600

Before FRANCISCO C. PRATS, RYAN H. FLAX and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a vaccine composition. The Examiner rejected the claims on appeal under 35 U.S.C. § 103(a) as obvious.

We affirm.

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[1] According to Appellants, the real party in interest is Australian Poultry CRC Pty Limited. App. Br. 3.

STATEMENT OF THE CASE

The Specification states that it was "known that vaccine compositions comprising attenuated pathogenic microorganisms such as bacteria or viruses are effective in producing a protective immune response in vaccinated animals and humans." Spec., p. 1, ll. 23–25. Typically, "attenuation of pathogenic organisms for use in a vaccine is achieved by complete or partial removal of one or more virulence factors such that the organism is no longer pathogenic." *Id.* at p. 1, ll. 30–32. The Specification asserts that virulence factors like toxins are obvious targets for attenuation, but factors that were not known to be "virulence factors" are "not obvious targets for attenuation." *Id.* at p. 2, ll. 9–10.

The Specification explains that ATP binding cassette ("ABC") transporters – "membrane proteins that function to translocate substrates across extra- and intra-cellular membranes" – "are not commonly thought of as virulence factors." *Id.* at p. 2, ll. 12–15. The Specification then asserts that "the present invention is predicated on the surprising finding that a loss of function mutation of an ABC-transporter gene in pathogenic organisms attenuated the pathogenic organisms although the attenuated organisms remained immunogenic and persisted in the subject as assessed in a host-disease model system." *Id.,* at p. 2, ll. 19–24.

Claims 24, 40–43, and 45–50 are on appeal.[2] Claim 24 is illustrative and reads as follows:

[2] In the Examiner's Answer, the Examiner withdrew the pending rejection of claim 44 under 35 U.S.C. § 103(a). Ans. 2. The patentability of claim 44 is, thus, no longer a part of this appeal.

> 24. A vaccine composition comprising an immunogenically effective amount of attenuated bacteria and a pharmaceutically acceptable carrier, wherein:
>
> the attenuated bacteria are attenuated by a mutation in an Oligopeptide Transport ATP-Binding Protein OppD (OppD) gene,
>
> the mutation renders the OppD protein encoded by the OppD gene non-functional, and
>
> the attenuated bacteria can persist in a subject to which the vaccine is administered.

The Examiner rejected claims 40–43, and 45–50 under 35 U.S.C. § 103(a) as obvious over the combination of Green,[3] Podbielski,[4] Hogarth[5] and Garmory.[6]

FINDINGS OF FACT

1. Garmory discloses:

> The purpose of this review is to demonstrate the possibility of targeting ABC transporters for the development of antibacterial vaccines and therapies. Traditionally, bacterial ABC transporters have been considered to play roles in nutrient uptake and drug resistance. However, there is increasing evidence that

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[3] Green et al., *A Peptide Permease Mutant of Mycobacterium bovis BCG Resistant to the Toxic Peptides Glutathione and S-Nitrosoglutathione,* 68(2) INFECTION AND IMMUNITY 429–36 (2000) ("Green").

[4] Podbielski et al., *Molecular Characterization of Group A Streptococcal (GAS) Oligopeptide Permease (Opp) and its Effect on Cystein Protease Production,* 21(5) MOLECULAR MICROBIOLOGY 1087–99 (1996) ("Podbielski").

[5] Hogarth et al., *Genetic Organization of the Oligopeptide Permease (opp) Locus of Salmonella Typhimurium and Escherichia Coli,* 153(3) J. BACTERIOL. 1548–51 (1983) ("Hogarth").

[6] Garmory et al., *ATP-Binding Cassette Transporters Are Targets for the Development of Antibacterial Vaccines and Therapies,* 72(12) INFECTION AND IMMUNITY 6757–63 (2004) ("Garmory").

> these transport systems play either direct or indirect roles in the virulence of bacteria.

Garmory 6758.

2. Garmory discloses: "the studies described in this review indicate that ABC transporter proteins may be suitable targets for the development of antibacterial vaccines, either through the development of live attenuated bacteria or through the development of protein- and DNA-based subunit vaccines." *Id.* at 6762.

3. Garmory discloses:

> The roles of ABC transporters in virulence of pathogenic bacteria have been attributed to the requirement for uptake of various nutrients. Several examples have been identified by using signature-tagged mutagenesis (STM), a technique designed to enable large-scale screening of bacterial mutants for organisms that have an attenuated phenotype. . . . Multiple animal infection models have also been used for STM to identify genetic loci that may be universally important for bacterial survival in vivo. When this approach was used with a number of *Staphylococcus aureus* models of infection, the largest gene class identified included genes encoding amino acid or oligopeptide transporters. ***For example, an oppC mutant was attenuated in multiple animal models.*** The *oppC* gene encodes a permease component of an oligopeptide transport system, Opp. In a separate study, STM was used to identify clones of *S. aureus* with mutations in genes with homology to ***oppD and oppF, which are genes that encode the ABC-containing proteins of the same oligopeptide ABC transport system.***

Id. at 6758 (emphasis added).

4. Green discloses: "Using sequences from the available genome database for *Mycobacterium tuberculosis* H37Rv, the oligopeptide permease operon *(oppBCDA)* of *Mycobacterium bovis* BCG was cloned from a cosmid

library. An *opp* mutant strain was constructed by homologous recombination with an allele of *oppD* interrupted by kanamycin and streptomycin resistance markers." Green Abstract.

5. Podbielski discloses: "To study the molecular and biological functions of the GAS [Group A Streptococcal] opp operon, the Opp-associated ATPase function was disrupted. . . . Insertional mutagenesis utilizing the vector pSF152 was performed which resulted in a truncated oppD gene and eliminated oppF expression." Podbielski 1091.

6. Hogarth discloses complementation experiments using bacteria with mutations to opp genes, including oppD. Hogarth 1548.

ANALYSIS

Appellants argue claims 24, 40–43, and 45–50 together as a group. We designate claim 24 as representative of the group.

OppD is a gene encoding an ABC transporter protein. The Examiner found that Green, Podbielski and Hogarth each disclosed a strain of bacteria with an oppD mutation. Ans. 2–3. The Examiner thus concluded that Green, Podbielski, and Hogarth met all of the limitations of claim 24 with the exception of a "pharmaceutical carrier." *Id.* at 3.

The Examiner found that Garmory disclosed that "ABC transporter proteins may be suitable targets for the development of antibacterial vaccines, either through the development of live attenuated bacteria (see page 6762, left column) or through the development of protein and DNA based subunit vaccines (see page 6760, right column)." *Id.* Garmory further disclosed that "mice immunized with a *Brucella abortus* mutant having a deletion in a virulence gene encoding that ABC-containing protein ExsA

exhibited superior protective immunity against virulent *B. abortus* challenge." *Id.*

Based on the combined teachings of Garmory, Green, Podbielski, and Hogarth, the Examiner concluded:

> it would have been obvious to one of skill in the art, at the time of invention, to use the composition comprising oppD mutants as taught by Green et al 2000 or Podbielski et al or Hogarth et al in an immunogenic composition comprising pharmaceutical carrier because Garmory et al suggests ABC transporter proteins may be suitable targets for the development of antibacterial vaccines, either through the development of live attenuated bacteria (see page 6762, left column) or through the development of protein- and DNA-based subunit vaccines (see page 6760, right column).

Id. We agree with the Examiner that the claimed composition would have been obvious over the combination of Garmory, Green, Podbielski, and Hogarth and address Appellants' arguments below.

Appellants argue that while Green, Podbielski, and Hogarth "disclose the generation and characterization of certain bacterial strains comprising *opp* mutations[,] . . . ***bacteria having a mutation rendering a certain gene product non-functional are not necessarily 'attenuated.'"*** App. Br. 8. Appellants contend that Garmory describes "a vaccine that is based on bacteria with a non-functional ABC ***exopolysaccharide*** transporter (exsA protein)," and that "[t]his is ***an entirely different class of ABC transporter*** than OppD, which is an ABC ***peptide*** transporter." *Id.* at 10. Appellants point to Garmory's teaching that ABC transporters "comprise one of the largest protein families" and that ABC transporters are "functionally diverse, covering a variety of different biological roles such as membrane transport,

RNA translation, and DNA repair and [are] involved in a very wide range of substrates including nucleic acids, nucleotide triphosphates, sugars, lipids, sterols, drugs, oligopeptides, ATP/GTP, and numerous other metabolic products." *Id.* Given the large and functionally diverse nature of the ABC protein family, Appellants contend that the skilled artisan would not reasonably have expected that "immunogenically effective amounts of ***attenuated OppD mutant bacteria*** could be generated and combined with a pharmaceutically acceptable carrier in order to arrive at the claimed vaccine composition." *Id.* at 10–11.

We are not persuaded. Garmory teaches that ABC transporter proteins play a role in the virulence of bacteria. FF1; *see also* Garmory 6758–59 (under section heading "ABC transporters have roles in bacterial virulence"). Garmory further teaches that ABC transporter proteins may be "suitable targets for the development of antibacterial vaccines . . . through the development of live attenuated bacteria . . . ." FF2. While Garmony does not disclose the use of oppD mutants as a vaccine, Garmory does disclose that a mutation to the oppC gene attenuated *Staphylococcus aureus* in multiple animal models. FF3. And Garmony further discloses that oppD encodes proteins of the same transport system as oppC. *Id.* In view of these teachings, we find that a skilled artisan would reasonably have expected that a mutation to the oppD gene would attenuate bacteria. Given this expectation, it would have been obvious to incorporate the oppD mutant bacteria of Green, Podbielski, or Hogarth with a pharmaceutically acceptable carrier in a vaccine. Appellants' arguments regarding the size and diversity of the genus of ABC transporter proteins and regarding Garmory's teaching of a vaccine from a different class of ABC transporter protein are not

persuasive because, in view of the above discussed teachings of Garmory, they would not have diminished the expectations of the skilled artisan with respect to the attenuating effects of mutations of oppD.

Appellants argue that because "Green, Podbielski, and Hogarth fail to teach about the immunogenic properties of the bacteria or about the capacity of the bacteria to persist in a subject, there is no basis for the Examiner's assumption that the compositions allegedly taught by the cited references comprise an ***immunogenically effective amount*** of attenuated bacteria." App. Br. 7. We find this argument unpersuasive because the Examiner relies upon a combination of references – not Green, Podbielski, or Hogarth alone – to render the claims obvious. *See, In re Merck & Co.,* 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references."). As discussed above, Garmory suggests incorporating oppD mutant bacteria, like that disclosed in Green, Podbielski, and/or Hogarth, with a pharmaceutically acceptable carrier in a vaccine. This suggestion encompasses an "immunogenically effective amount of attenuated bacteria," particularly given the breadth of the term "immunogenically effective amount." *See,* Spec. p. 17 ("The vaccine composition may comprise any dose of bacteria, sufficient to evoke an immune response" including specified amounts of 10^3 and 10^{19} attenuated bacteria.).

Accordingly, we affirm the Examiner's determination that claim 24 is obvious under 35 U.S.C. § 103(a) over the combination of Green, Podbielski, Hogarth, and Garmory. Because they were not argued separately, claims 40–43, and 45–50 fall with claim 24.

SUMMARY

For the reasons provided herein and those set forth in the Examiner's Answer and the Final Office Action, the rejection of claims 24, 40–43, and 43–50 under 35 U.S.C. § 103(a) as obvious over the combination of Green, Podbielski, Hogarth, and Garmory is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1).

AFFIRMED